19 ~~26~~. (New) The method of claim 17 ~~24~~, wherein the pharmaceutically acceptable carrier is suitable for oral delivery.

20 ~~27~~. (New) The method of claim 17 ~~24~~, wherein the pharmaceutically acceptable carrier is suitable for intravenous delivery.

21 ~~28~~. (New) The method of claim 17 ~~24~~, wherein the pharmaceutically acceptable carrier is suitable for parenteral delivery.

22 ~~29~~. (New) The method of claim 17 ~~24~~, wherein the pharmaceutically acceptable carrier is suitable for intradermal delivery.

23 ~~30~~. (New) The method of claim 17 ~~24~~, wherein the pharmaceutically acceptable carrier is suitable for subcutaneous delivery.

24 ~~31~~. (New) The method of claim 17 ~~24~~, wherein the pharmaceutically acceptable carrier is suitable for topical delivery.

25 ~~32~~. (New) The method of claim 17 ~~24~~, wherein the compound is in the form of a dosage unit.

26 ~~33~~. (New) The method of claim 25 ~~32~~, wherein the dosage unit contains 10 to 1500 mg of the compound.

27 ~~34~~. (New) The method of claim 25 ~~23~~ or 26 ~~33~~, wherein the dosage unit is a tablet or capsule.

Remarks

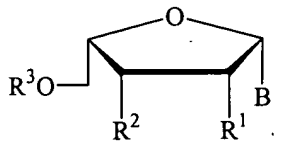
Original claims 3 and 7-10 as now amended and new claims 13-34 will be pending after entry of this amendment; these claims are directed to methods to treat hepatitis B virus in a host using β-L-2'-deoxycytidine and/or β-L-thymidine. Support for these claims can be found on

page 8, lines 13-16 of the specification. Claims 14-23 and 25-34 are directed to methods to treat HBV using β-L-2'-deoxycytidine or β-L-thymidine, respectively, with pharmaceutically acceptable carriers. Support for these claims can be found on page 48, lines 10-16 and page 49, lines 3-5 of the specification.

Rejections under 35 U.S.C. § 102 and 103

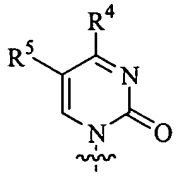
Original claims 1-10 and 13 were rejected under 35 U.S.C. § 102 on the basis that U.S. Patent No. 5,559,101 ('101) to Weis et al. discloses β-L-2'-deoxyinosine for the treatment of a variety of diseases (that do not include hepatitis B). Similarly, original claims 11 and 12 were rejected under 35 U.S.C. § 102 on the basis that U.S. Patent No. 5,939,402 ('402) to Weis et al. discloses β-L-2'-deoxyinosine. Weiss does not disclose the claims as now presented, which are limited to the method to treat hepatitis B with β-L-2'-deoxycytosine and β-L-thymidine.

Original claims 1-12 were rejected under 35 U.S.C. § 102(b) on the basis that European Patent Application No. 0 352 248 A1 ('248) to Johansson et al (the Medivir application) discloses the nucleosides of the present invention for the treatment of hepatitis B. The Examiner is respectfully requested to reconsider this rejection in light of the claims now presented, which are directed to the use of β-L-2'-deoxycytosine and β-L-thymidine. The '248 patent discloses L-ribofuranosyl compounds which include analogs of the formula **I**:



(I)

wherein R^1 and R^3 can be hydrogen, R^2 can be OH and B is adenine, guanine, hypoxanthine, 2,6-diaminopurine or

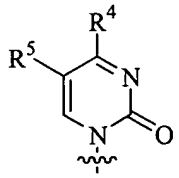


wherein:

R^4 is OH or NH_2, and

R^5 is H, CH_3 or C_2H_5.

However, there is an express limitation in the disclosure of the '248 specification and claims which states that when the nucleoside is the β anomer, R^1 is H, R^2 is OH, and R^3 is OH, B is limited to adenine, guanine, hypoxanthine, 2,6-diaminopurine or



wherein

R^5 is C_2H_5 when R^4 is OH and

R^5 is CH_3 or C_2H_5 when R^4 is NH_2;

Therefore, in the '248 patent, B specifically **cannot** be thymine or cytosine, because the Medivir text specifically excluded it. The only portion of the entire publication that specifically mentions the claimed β-2'-L nucleosides is in the prior art section where they cite Holy et al. Coll. Czech. Chem. Commun., **1972**, *37*, 4072-4087 for syntheses of β-L-thymidine and β-2'-deoxy-L-cytidine.

Original claims 1-10 were rejected under 35 U.S.C. § 103(a) as obvious in light of the combination of European Patent '248 with von Janta-Lipinski et al. J. Med. Chem., **1998**, *41* (12), 2040-2046 and Lin et al. J. Med. Chem., **1996**, *39* (9), 1757-1759. As discussed above, the claims as now presented are not disclosed, and in fact, are explicitly excluded from '248 patent. The von Janta-Lipinski reference discloses the biological activity of the triphosphate of β-L-thymidine (but not β-L-2'-dC) as a nucleoside inhibitor of endogenous DNA polymerases of HBV and DHBV. However, only triphosphorylated β-L-thymidine was evaluated, not the claimed unphosphorylated form, and there is no comment in the article on whether those β-L-nucleosides are phosphorylated in cells or *in vivo* or, more importantly, there is no comment on the efficacy of phosphorylation of β-L-thymidine *in vivo*. Because of this, the article does not

teach one of skill in the art that β-L-thymidine would have any hepatitis B activity in a cell or *in vivo*.

The prevailing data at the time, reported by Spadari, et. al. ("L-Thymidine is Phosphorylated by Herpes Simplex Virus Type 1 Thymidine Kinase and Inhibits Viral growth," J. Med. Chem., **1992**, *35*, 4214-4220, copy enclosed), indicated, although incorrectly, that while β-L-dT was a substrate for herpes simplex thymidine kinase, it was not a substrate for cellular kinases. On the basis of the Spadari article, scientists believed at the time that β-L-dT would not be phosphorylated in a cell-based system or *in vivo*. Thus, the combination of the von Janta-Lipinski and Spadari taught at the relevant time that while the triphosphate of β-L-dT is an inhibitor of HBV DNA polymerase in a laboratory cell-free environment, the triphosphate is not produced inside the cell because it is not a recognized substrate for cellular kinases, and thus the parent unphosphorylated compound would be useless in a cell or *in vivo* since it couldn't be activated.

The scientific and patent literature is filled with examples of synthetic nucleosides that in a triphosphorylated form are able to inhibit a polymerase or reverse transcriptase, but have little or no activity *in vivo* because of either the inability of the synthetic nucleosides to be effectively phosphorylated in the body, or because they are metabolized in a manner that doesn't allow the triphosphorylated form to exist long enough to have a therapeutic effect. Because of this, one cannot predict or even have a reasonable assurance of *in vivo* activity from the *in vitro* inhibition of an enzyme when presented artificially in the activated state under laboratory conditions.

The correlation between antiviral activity of a nucleoside triphosphate in an *in vitro* polymerase assay and prediction of antiviral activity in cell-based assays or *in vivo* against a replicating virus such as HBV was not established in the von-Janta-Lipinski article. To the contrary, the authors recommended further evaluation of the chemical compound β-L-FTdR as a selective inhibitor of HBV, which as a synthetic triphosphate derivative (β-L-FTTP) was the most active against the HBV and duck polymerases. However, β-L-FTdR has now also been

shown to be inactive against the replicating virus in cell-based systems or *in vivo* (Bryant, et.al. "Antiviral L-Nucleosides Specific for Hepatitis B Virus Infection," Antimicrobial Agents and Chemotherapy **2001**, *45*, 229-235), copy enclosed.

The Applicants of the present invention have shown that β-L-dT is a substrate for two cellular kinases, deoxycytidine kinase and thymidine kinase 1 with subsequent activation to the triphosphate derivative in human hepatocytes. Instead of anticipating or rendering obvious the present application, the von-Janta-Lipinski and Spadari references support the patentability of the claim for the use of β-L-dT to treat HBV infection.

The Lin article describes the use of 2',3'-dideoxy-2',3'-didehydro-β-L-cytidine and 2',3'-dideoxy-2',3'-didehydro-β-L-5-fluoro-cytidine for the treatment of hepatitis B (HBV). These compounds are non-naturally occurring nucleoside analogs **in which the hydroxyl moieties at the 2' and 3' positions of the ribose ring are absent**. This article does not describe the use of β-L-thymidine and β-L-2'-deoxycytidine for any therapeutic indication.

Further, the 3'-hydroxyl group of β-L-2'-deoxyribose nucleosides confers unique specificity for anti-hepatitis B activity. Both 2',3'-dideoxy and 2',3'-dideoxy-2',3'-didehydro compounds exhibit less selectivity toward hepatitis B than the present β-L-2'-deoxyribose nucleosides, and typically also exhibit some anti-HIV activity. Specifically, L-dC and L-dT have been screened against fifteen different RNA and DNA viruses. The β-L-2'-deoxynucleosides inhibited hepadnaviruses but had no activity against HIV, herpes simplex types 1 and 2, varicella-zoster virus, Epstein Barr Virus (EBV), human cytomegalovirus, adenovirus type 1, influenza A and B viruses, measles, and other viruses at up to 200 micromolar (Bryant, et.al. "Antiviral L-Nucleosides Specific for Hepatitis B Virus Infection," Antimicrobial Agents and Chemotherapy **2001**, *45*, 229-235). It is an advantage to administer a drug for hepatitis B treatment that does not exhibit activity against another virus, because cessation of the drug for reasons associated with the second viral infection can cause a life-threatening hepatitis B flare in the co-infected patient. Alternatively, a flare of the other virus could occur. Therefore, there is

an advantage to the patient of a drug that shows a unique profile for hepatitis B, which then allows the care provider to independently treat a co-infection such as HIV or EBV without effect on the hepatitis B regimen.

Rejections under 35 U.S.C. § 112

The Examiner rejected originally pending claims 1-12 on the basis that the term "prodrug" is unclear. The Examiner's attention is directed to the fact that the term prodrug is specifically defined on page 11 as a compound that is converted into the claimed nucleoside on administration *in vivo*. Nonlimiting examples are pharmaceutically acceptable salts, the 5' and N^4 or N^6 acylated or alkylated derivatives and the 5'-phospholipids and 5'-ether lipids. Applicants are pursing the use of prodrugs in the companion case U.S. Serial No. 09/459,150.

Original claims 1 and 8-9 were rejected under 35 U.S.C. §112, second paragraph, allegedly because the terms "CO-alkyl" and the like can imply mono or diradicals. Applicants respond that those of even below ordinary skill in the art can identify and appreciate an open valence state and would not fail to understand the meaning of C(O)alkyl, etc as indicating a moiety with a completed valence. There is nothing in the text to suggest that the claimed compounds have open valence states. Applicants are pursing the use of such compounds in the companion case U.S. Serial No. 09/459,150.

Claims 1 and 8-9 were rejected under 35 U.S.C. §112, second paragraph, allegedly because the term "optionally substituted" is unclear. The term "optionally substituted" has also been deleted, as all bases in the present claims are specifically defined. The examiner has likewise objected to other language that was in the claims as originally presented but not in the claims as now presented.

Claim 10 was rejected under 35 U.S.C. §112, second paragraph, allegedly because the acronyms 3TC, FTC, L-FMAU, DAPD, BMS and PMEA are unclear. According to the Examiner's suggestion, Applicants have amended the present claims to clarify the meaning of

the acronyms 3TC, FTC, L-FMAU, DAPD, BMS and PMEA, to define the known antiviral agents in accordance with their complete name.

The claims as originally presented were rejected under the doctrine double patenting in light of the claims presented in U.S.S.N. 09/459,150. A response to Office Action with amended claims is being submitted in the '150 application today. The claims in the '150 application are not the same as, but overlap with the claims presented herein. Therefore, Applicants enclose a Terminal Disclaimer that disclaims the terminal portion of any patent that issues from this application that extends beyond the term of a patent issuing from the '150 application, and that disclaims the terminal portion of any patent that issues from the '150 application that extends beyond the term of a patent issuing from this application.

Respectfully submitted,

Sherry M. Knowles, Esq.
Registration No. 33,052

Date: August 27, 2001

Enclosure: Marked up version of amendment

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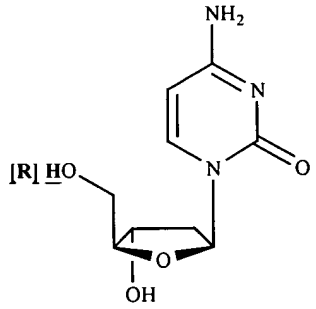
Version with Markings to Show Changes Made

In the Claims

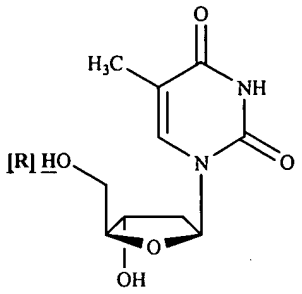
Claims 3 and 7-10 have been amended as follows:

3. (Once Amended, Marked Up) [~~The~~] A method [~~of claim 1, wherein the 2'-deoxy-β-L-erythro-pentofuranonucleoside is~~] **for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of** β-L-2'-deoxycytidine [~~or pharmaceutically acceptable salt or prodrug thereof~~] of the formula:



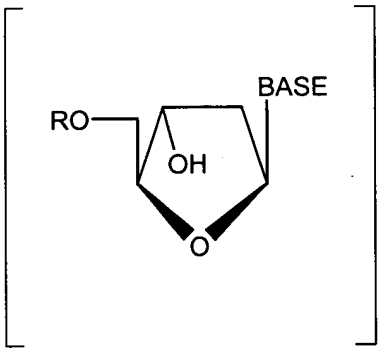
[~~wherein R is H, mono, di or tri phosphate, amino acid residue, acyl, or alkyl, or a stabilized phosphate derivative (to form a stabilized nucleotide prodrug)~~] **or pharmaceutically acceptable salt thereof**.

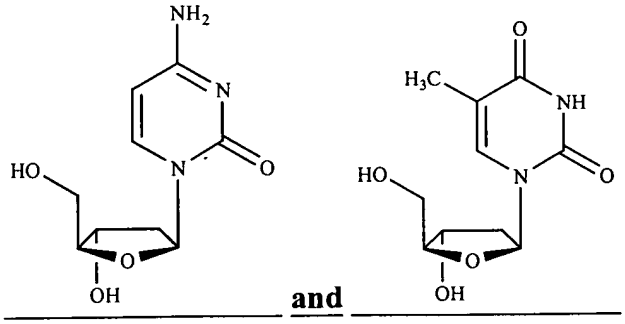
7. (Once Amended, Marked Up) [~~The~~] A method [~~of claim 1, wherein the 2'-deoxy-β-L-erythro-pentofuranonucleoside is~~] **for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of** β-L-thymidine [~~or pharmaceutically acceptable salt or prodrug thereof~~] of the formula:



~~[wherein R is H, mono, di or tri phosphate, amino acid residue, acyl, or alkyl, or a stabilized phosphate derivative (to form a stabilized nucleotide prodrug)]~~ **or pharmaceutically acceptable salt thereof**.

8. (Once Amended, Marked Up) A method for ~~[treating a host infected with hepatitis B]~~ **the treatment or prophylaxis of a hepatitis B virus infection in a host** comprising administering an effective amount of ~~[two or more anti-HBV biologically active 2'-deoxy-β-L-erythro-pentofuranonucleosides or a pharmaceutically acceptable salt or prodrug thereof in combination or alternation, wherein the 2'-deoxy-β-L-erythro-pentofuranonucleosides have the formula]~~ **a combination of the following nucleosides:**

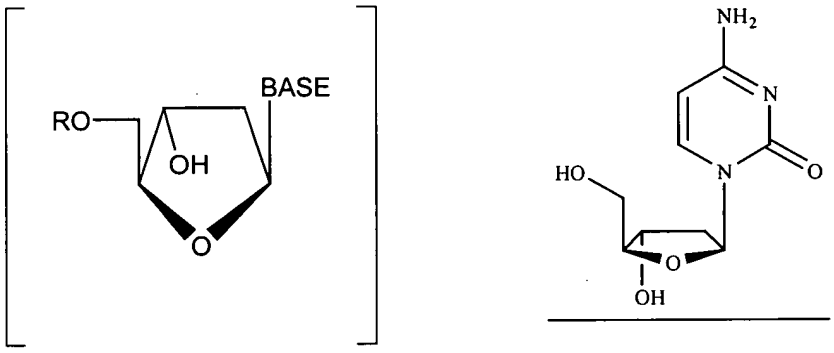




and

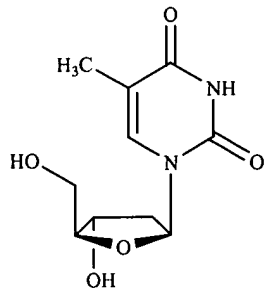
~~[wherein R is selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, amino acid residue, mono, di, or triphosphate, or a phosphate derivative; and BASE is a purine or pyrimidine base which may be optionally substituted]~~ **or a pharmaceutically acceptable salt thereof**.

9. (Once Amended, Marked Up) A method for ~~[treating a host infected with hepatitis B]~~ **the treatment or prophylaxis of a hepatitis B virus infection in a host** comprising administering an effective amount of ~~[an anti-HBV biologically active 2'-deoxy-β-L-erythro-pentofuranonucleoside or a pharmaceutically acceptable salt or prodrug thereof in combination or alternation with an additional anti-hepatitis B agent, wherein the 2'-deoxy-β-L-erythro-pentofuranonucleoside has]~~ **a compound of** the formula:



~~[wherein R is selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, amino acid residue, mono, di, or triphosphate, or a phosphate derivative; and BASE is a purine or pyrimidine base which may be optionally substituted]~~ **or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of a compound selected from the group consisting of β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), *cis*-2-hydroxymethyl-5-(5-fluoro-cytosin-1-yl)-1,3-oxathiolane (FTC), β-L-2'-fluoro-5-methyl-arabinofuranolyluridine (L-FMAU), β-D-2,6-diaminopurine dioxolane (DAPD), famciclovir, penciclovir, 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), 9-[2-(phosphono-methoxy)ethyl]adenine (PMEA, adefovir, dipivoxil); lobucavir, ganciclovir and ribavirin.**

10. (Once Amended, Marked Up) [~~The~~] A method [~~of claim 9, wherein the additional anti-hepatitis B agent is~~] **for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:**



or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of a compound selected from the group consisting of **β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane** (3TC), ***cis*-2-hydroxymethyl-5-(5-fluoro-cytosin-1-yl)-1,3-oxathiolane** (FTC), **β-L-2'-fluoro-5-methyl-arabino-furanolyluridine** (L-FMAU), **β-D-2,6-diaminopurine dioxolane** (DAPD), famciclovir, penciclovir, **2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one (entecavir,** BMS-200475), **9-[2-(phosphonomethoxy)-ethyl]adenine** (PMEA, [~~bis-pom PMEA (~~] adefovir, dipivoxil); lobucavir, ganciclovir and ribavirin.